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ORIGINAL ARTICLE

Right ventricular stroke work index from echocardiography in patients with pulmonary arterial hypertension—the role in short-term follow-up assessment

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Abstract

Aims

Right ventricular (RV) failure causes high mortality in patients with pulmonary arterial hypertension (PAH). RV stroke work index (RVSWi) poses as a potential predictor of outcome. We evaluated how RVSWi by echocardiography (ECHO) or right heart catheterization (RHC) is altered following PAH treatment and if RVSWi is an indicator of outcome in PAH.

Methods and results

Fifty-four patients with PAH performed ECHO and RHC (median, 0 days between examinations) at baseline and treatment follow-up. $RVSWi_{RHC}$ was computed as (mPAP-mRAP)×SVi_{RHC}, (mPAP, mean pulmonary arterial pressure; mRAP, mean right atrial pressure; SVi, stroke volume indexed to body surface area). ECHO-derived RVSWi was calculated as $RVSWi_{ECHO\text{-}Mean} = TR_{mean}PG \times SVi_{ECHO}$ and $RVSWi_{ECHO\text{-}Max} = TR_{max}PG \times SVi_{ECHO}$ ($TR_{mean}PG$ and $TR_{max}PG$: tricuspid regurgitant mean and maximum pressure gradient). Invasive sPAP, mPAP, and pulmonary vascular resistance decreased and SVi increased from baseline to follow-up ($P < 0.01$ for all). $RVSWi_{RHC}$ and $RVSWi_{ECHO}$ (Mean and Max) did not differ from baseline to follow-up ($P > 0.05$). Forty patients died during 109 ± 24 months. In univariate Cox proportional hazard analysis, age > 65 years, 6-minute-walk test < 160 m, WHO class III-IV and indexed right atrial volume were associated with long-term mortality, but none of the RVSWi methods. In multivariate analysis with clinical parameters, both $RVSWi_{ECHO}$ methods were independently associated with mortality.

Conclusion

The RVSWi methods did not differ from baseline to short-term follow-up and were not associated with long-term outcomes in univariate analysis. However, baseline $RVSWi_{ECHO}$ was associated with mortality when adjusting for clinical parameters.

Keywords

pulmonary arterial hypertension • echocardiography • right ventricular stroke work index • clinical follow-up • outcome

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Introduction

Right ventricular (RV) failure is the major cause of death in patients with pulmonary arterial hypertension (PAH).[1–4] PAH is characterized by progressive pulmonary vasoconstriction and vascular remodelling resulting in both increased pulmonary vascular resistance (PVR) and RV afterload.[5] Hence, guidelines recommend a comprehensive haemodynamic assessment as well as an extensive validation of RV function.[4,6–10]

Transthoracic echocardiography (ECHO) is the first-line modality for hemodynamic and functional evaluation. Nevertheless, owing to complex anatomy and at times suboptimal acoustic conditions for complete image acquisition, it is still challenging to objectively evaluate RV function by echocardiography.[11–13] Recently, a novel echocardiographic algorithm for quantitative estimation of pulmonary artery wedge pressure (PAWP) and PVR has been proposed, showing high diagnostic accuracy in patients with heart failure and pulmonary hypertension, even in the presence of atrial fibrillation.[14] So far there is no echocardiographic parameter or index that exclusively reflects the complexity of RV hemodynamics. Right heart catheterization (RHC) is the gold standard for haemodynamical assessment and required to confirm the diagnosis of PAH as well as to assess the severity of disease.[8–10] Still, standard RHC measures—such as pulmonary arterial pressures and PVR—are not strong predictors of outcome,[8] wherefore better indicators of haemodynamic measures of outcome are warranted. A more complex, multiparametric evaluation of RV function including exercise echocardiography, such as that provided by Gargani *et al.* may be prognostically relevant but is time-consuming and limited by technical aspects like RHC as well as scarcely validated in PAH.[15]

Pairing pressure and volume measurements into pressure-volume loops allows computation of RV stroke work index (RVSWi); an index for RV function which integrates afterload, preload, contractility, and ventricular-vascular coupling. RVSWi by RHC ($RVSWi_{RHC}$) has been proposed as determinant of outcome.[16–20] However, computation of RVSWi requires invasive data and conductance catheters to generate pressure-volume loop, hence limiting the accessibility to dedicated expert centres. Previously, echocardiographic-derived RVSWi methods ($RVSWi_{ECHO}$) have been associated with $RVSWi_{RHC}$ in treatment-naïve PAH patients.[21]

Still, it is unknown how RVSWi changes after treatment from baseline investigation of PAH. Therefore, the aim of this study is to investigate if RVSWi, assessed by echocardiography and RHC in those patients, changes following treatment. Furthermore, we aimed to investigate if RVSWi at baseline is associated with mortality.

Methods

Study population

Seventy consecutive adult patients with treatment-naïve PAH, referred to RHC for *de novo* diagnosis and management of PAH, examined from 1 January 2012, to 31 December 2019, at a tertiary PAH centre (Skane University Hospital, Lund, Sweden) were retrospectively assessed. The diagnosis of PAH was confirmed by RHC, in concordance with contemporary guidelines at the time[6–9] and in the absence of other causes of pre- and post-capillary pulmonary hypertension (PH). In accordance with the current guidelines at inclusion, PAH was defined as mPAP ≥ 25 mmHg, pulmonary artery wedge pressure (PAWP) < 15 mmHg and PVR > 3 Wood Units (WU),[7] and since January 2019, the new cut-off for mPAP > 20 mmHg was adopted.[22] In the latter study period, five patients were included, of which one patient had mPAP 23 mmHg, while the remaining had mPAP >25 mmHg. Patients were evaluated clinically, with six minute-walk test (6MWT), echocardiograms, RHC, blood samples, and World Health Organization functional class (WHO-FC). Medical records, echocardiograms, and invasive haemodynamic data were reviewed at baseline and short-term follow-up visits.

Inclusion criteria were *de novo* diagnosed PAH, adult patients > 18 years, a maximum of 7 days between echocardiography and RHC, and no clinical deterioration or treatment changes between the exams. Exclusion criteria were: dedicated PAH treatment ($n = 3$), poor echocardiographic image quality ($n = 4$), pacemaker ($n = 1$), non-adequate tricuspid spectral Doppler ($n = 1$), atrial fibrillation ($n = 2$), coronary artery by-pass surgery due to severe coronary vessel disease ($n = 1$), myocardial infarction with decreased left ventricular systolic function ($n = 1$), more than moderate valvular stenosis (aortic stenosis ($n = 2$), and mitral stenosis ($n = 1$). Thereby, leaving 54 patients included for baseline analysis (*Figure 1*).

A baseline visit was defined as the visit when the patients were diagnosed with PAH, typically on the day of RHC. PAH-specific treatment was initiated and optimized according to European Guidelines for pulmonary hypertension.[6–9] Short-term follow-up visit was performed 3 to 12 months after baseline as an outpatient visit or as a scheduled admission in concordance with local clinical routine. Exclusion criteria for follow-up exams were incomplete echocardiography exam ($n = 2$), non-adequate tricuspid spectral Doppler ($n = 1$), no RHC performed ($n = 1$), and death before follow-up ($n = 6$), thereby leaving 44 patients for follow-up analysis (*Figure 1*).

For survival analysis, patients were followed until 13 May 2024, and data were acquired from electronic medical records.

The study was endorsed by the regional department of the Swedish Ethical Review Authority (Dnr 2010/114, Dnr 2010/248 Dnr 2010/442) and complies with the Declaration of Helsinki. Written informed consent was obtained by the patients.

Right heart catheterization (RHC)

RHC was performed in local anaesthesia with an 8 French sheath being inserted by the Seldinger technique via the right jugular vein. A Swan-Ganz catheter was used to measure systolic (sPAP), mean (mPAP), and diastolic (dPAP) pulmonary arterial pressures. Mean right atrial pressure (mRAP) and pulmonary artery wedge pressure (PAWP) were acquired at free breathing as an average over several heartbeats. Stroke volume indexed (SVi) to body surface area (BSA) was obtained from thermodilution, and cardiac output (CO) was computed from SV and heart rate. PVR was computed as (mPAP-PAWP)/CO. Systemic non-invasive blood pressure was measured using an arm-cuff and sphygmomanometer. $RVSWi_{RHC}$ was calculated as (mPAP—mRAP)×SVi.[16–18,21]

Echocardiography

All patients underwent comprehensive two-dimensional transthoracic echocardiographic examinations using an iE33 platform (Philips Healthcare, Eindhoven, NL). Acquisition and assessment of echocardiographic measures were performed according to guidelines from the American Society of Cardiology.[23] An electronic echocardiographic database was used for storage and analysis of all echocardiographic images (Philips IntelliSpace Cardiovascular, Philips Healthcare, Eindhoven, NL).

Left ventricular (LV), left atrial (LA), and right atrial (RA) dimensions, areas and volumes were measured. LV ejection fraction was calculated by Biplane Simpson's method. SVi from left ventricular outflow tract (LVOT) was obtained by the formula: SVi_{ECHO} = (LVOT area × velocity–time integral from LVOT)/BSA.

Conventional RV functional parameters such as tricuspid annular plane systolic excursion (TAPSE), tricuspid S' velocity (S'), fractional area change (FAC) as well as RV longitudinal free wall strain (RVFWS) were assessed.[23,24] Trans-tricuspid regurgitant (TR) velocity

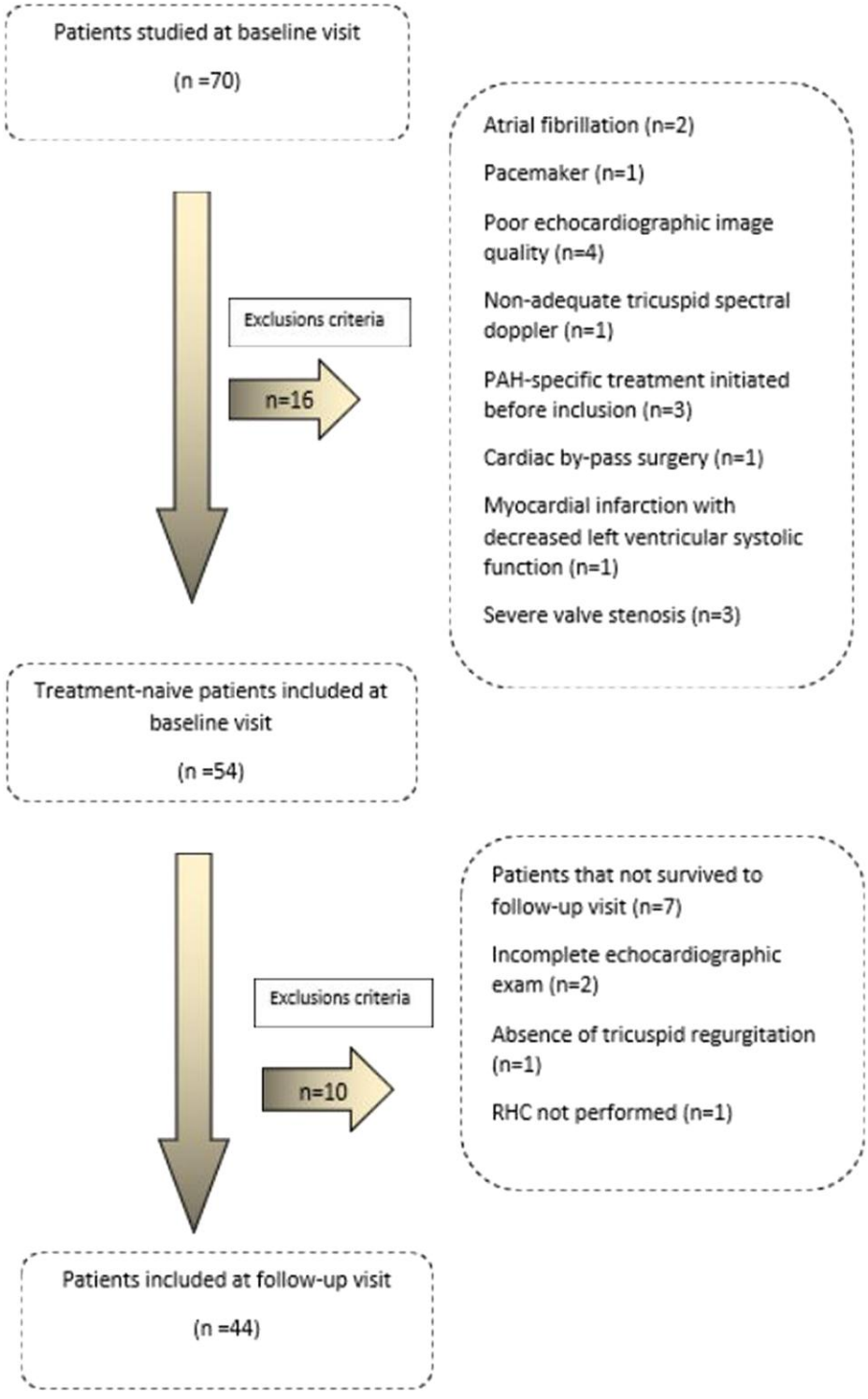

Figure 1 Participant exclusion criteria flow-chart at baseline and follow-up visit. PAH, Pulmonary arterial hypertension; RHC, right heart catheterization.

was used to estimate the RV-RA pressure gradient (PG) by using the modified Bernoulli equation.[25] Estimation of $sPAP_{ECHO}$ was derived from the maximum TR pressure gradient (TR_{maxPG}) (*Figure 2*) and adding estimated mean right atrial pressure ($mRAP_{ECHO}$), assessed from the diameter of the inferior vena cava (IVC) and its respiratory variability according to guidelines (i.e. 3 mmHg if the IVC diameter $\leq$ 2.1 cm with collapse > 50%, 8 mmHg if the IVC diameter < 2,1 cm with <50% collapse or IVC diameter > 2.1 cm with collapse < 50% and

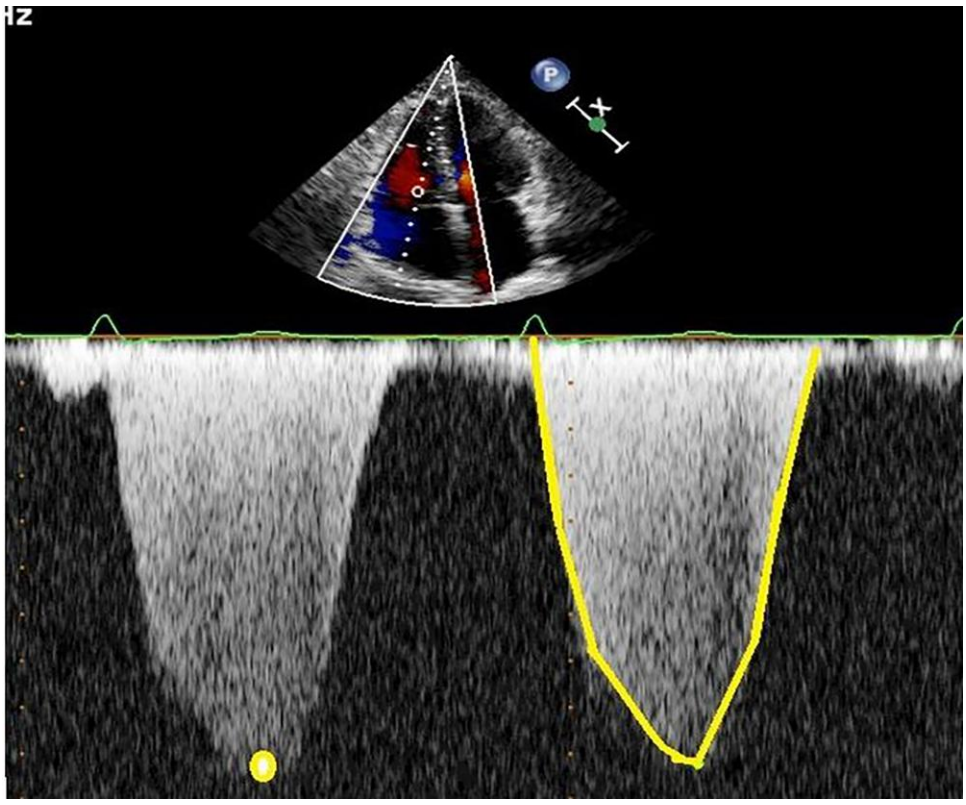

Figure 2 Echocardiographic illustration of measurement of maximum (yellow dot) and mean (yellow delineation) pressure gradients from a tricuspid regurgitation using continuous wave Doppler.

15 mmHg if the IVC diameter > 2.1 cm with < 50% collapse).[23] Estimated $mPAP_{ECHO}$ was based on mean TR pressure gradient (TR_{meanPG}) calculated by the velocity integral of the tricuspid regurgitant spectral Doppler curve (*Figure 2*) and adding estimated $mRAP_{ECHO}$ as described earlier.[7] RVSWi has been suggested and computed from invasive measurements of either sPAP or mPAP and with or without mRAP.[16,18–20,26,27] Previously presented $RVSWi_{ECHO}$ methods were calculated from the echocardiography-derived measurements including either TR_{maxPG}, TR_{meanPG}, or mRAP.[16,21] $RVSWi_{ECHO}$ was calculated using $sPAP_{ECHO}$ and $mPAP_{ECHO}$ as follows:

(1) $\mathbf{RVSWi_{ECHO\text{-}Max}} = (sPAP_{ECHO} - mRAP_{ECHO}) \times SVi_{ECHO}$
$= (TR_{maxPG} + mRAP_{ECHO} - mRAP_{ECHO}) \times SVi_{ECHO}$
$= TR_{maxPG} \times SVi_{ECHO}$.

(2) $\mathbf{RVSWi_{ECHO\text{-}Mean}} = (mPAP_{ECHO} - mRAP_{ECHO}) \times SVi_{ECHO}$
$= (TR_{meanPG} + mRAP_{ECHO} - mRAP_{ECHO}) \times SVi_{ECHO}$
$= TR_{meanPG} \times SVi_{ECHO}$.

These measurements were evaluated at baseline and at the follow-up clinical visits.

Six-minute-walk test and World Health Organization functional class

6MWT was performed standardized and assisted by an expert physiotherapist measuring the distance covered during 6 min.[28] Tests were performed in conjunction with RHC at baseline and follow-up visits.

World Health Organization functional class (WHO-FC) was assessed at baseline and follow-up visits.

Blood sampling and assay

Blood samples from a peripheral vein were acquired in all patients at diagnostic catheterization and repeated at follow-up visits. Blood was immediately transferred to a chilled glass tube containing disodium EDTA (1 mg/mL) and aprotinin (500 U/mL) and sent to the central laboratory in the hospital for analysis. Routine biochemistry, haematology, liver function tests, and plasma levels of N-terminal-pro-brain natriuretic peptide (NT-proBNP) were measured. Blood samples for systemic arterial blood oxygen saturation were taken from arteria radialis during RHC.

Statistical analysis

Data were expressed as median with inter-quartile range (IQR) owing to non-Gaussian distribution in many variables when assessed by the Shapiro-Wilk test. Categorical data were expressed in absolute numbers and proportions in percentage. Mann–Whitney *U* test, Wilcoxon Signed Rank test and Kruskal–Wallis test 1-way ANOVA were used for comparison.[29] Univariate Cox regression analysis was used to determine the associations to all-cause mortality. Multivariate Cox proportional hazard regression model with forward selection based on likelihood ratio statistics was performed individually for each RVSWi parameter, based on associations from the univariate analysis including age > 65 years, 6MWT <160 m, and WHO class III and IV ($P < 0.1$). Hazard ratio (HR) and 95% CI were calculated per unit for each independent continuous variable. Kaplan–Meier survival curve was created using quartiles of RVSWi at baseline. A two-tailed *P*-value <0.05 was considered statistically significant.[30] Statistical

Table 1 Demographic and clinical characteristics at baseline and follow-up visits

	Baseline ($n = 54$)	Follow-up ($n = 44$)
Demographic and clinical characteristics		
Sex (women/men)	36 (67)/18 (33)	32 (73)/12 (27)
Age (years)	69 [58–74]	69 [59–74]
BSA (m^2)	1.8 [1.6–2]	1.8 [1.6–2]
Etiological subclasses of pulmonary arterial hypertension		
Idiopathic PAH	30 (56)	25 (57)
Heritable PAH	3 (6)	2 (4)
PAH associated with CTD	17 (31)	14 (32)
PAH associated with portal hypertension	2 (4)	2 (5)
Drug and toxin-induced PAH	2 (4)	1 (2)
Comorbidities		
Diabetes	15 (28)	13 (30)
Hypertension	24 (44)	17 (39)
Coronary artery disease	10 (19)	8 (18)
Previous stroke	3 (5)	3 (7)
Thyroid disease	14 (26)	12 (27)
Functional capacity and laboratory parameters		
6 MWT (m)	245 [131–350]	288 [235–433]***
NT-proBNP (ng/L)	1698 [374–3147]	575 [252–1185]***
WHO functional class		
I	1 (2)	1 (2)
II	16 (30)	24 (55)
III	33 (61)	17 (39)
IV	4 (7)	2 (4)

Data are expressed as median [inter-quartile range] or as absolute numbers and proportion (percentage).
BSA, (body surface area); CTD, (connective tissue disease); 6-MWT, (6-minutes walking test); NT-proBNP, (brain natriuretic peptide); NYHA class, (New York Heart Association) functional classification for heart failure.
***$P < 0.001$

Table 2 At baseline visit, initiated PAH-specific treatment and other medications

PAH-specific medication	
Single therapy	26 (48)
Dual therapy	26 (48)
Triple therapy	1 (2)
Other medications	
Anticoagulation	7 (13)
Ca-channel blockers	12 (22)
Diuretics	26 (48)

Data are expressed as absolute numbers and proportion (percentage).

Table 3 Echocardiographic and right heart catheterization parameters at baseline and follow-up visit

	Baseline ($n = 54$)	Short-term follow-up ($n = 44$)	*P*-value
Echocardiography			
HR (beats/min)	80 [73–93]	77 [71–88]	**0.04**
LVEDV (mL)	53 [38–78]	75 [55–96]	**< 0.001**
LVESV (mL)	20 [12–29]	28 [17–40]	**< 0.001**
LVEF (%)	61 [55–67]	62 [52–71]	0.2
LA Volume/BSA (mL/m^2)	22 [17–28]	29 [23–38]	**< 0.001**
RA area (cm^2)	22 [18–26]	23 [18–27]	0.2
RA volume/BSA (mL/m^2)	39 [31–52]	41 [32–54]	0.2
RV inflow (mm)	49 [43–56]	46 [38–51]	0.1
RV mid (mm)	40 [31–44]	38 [30–44]	0.7
RVFAC (%)	27 [17–33]	30 [27–43]	**< 0.001**
TAPSE (mm)	18 [14–20]	19 [16–21]	**0.003**
S´ (cm/s)	10 [8–12]	11 [9–13]	**0.006**
RVFWS (%)	16 [10–20]	18 [13–25]	**0.01**
TAPSE/sPAP (mm/mmHg)	0.21 [0.16–0.3]	0.28 [0.21–0.46]	**< 0.001**
SVi (mL/m^2)	26 [22–36]	34 [28–42]	**< 0.001**
CO (L/min)	4 [3.2–4.9]	4.7 [4–5.4]	**< 0.001**
CI ($L/min/m^2$)	2.2 [1.8–2.7]	2.5 [2.1–3.1]	**< 0.001**
TR maximum velocity (m/sec)	4.2 [3.8–4.5]	3.6 [4.2–4.1]	**< 0.001**
TR maximum gradient (mmHg)	70 [55–80]	55 [45–69]	**< 0.001**
TR mean gradient (mmHg)	40 [32–46]	34 [28–41]	**< 0.001**
sPAP (mmHg)	76 [62–85]	61 [49–74]	**< 0.001**
mRAP (mmHg)	8 [3–8]	3 [3–8]	0.4
RHC			
sPAP (mmHg)	75 [68–88]	65 [47–74]	**< 0.001**
mPAP (mmHg)	45 [39–56]	40 [29–45]	**< 0.001**
PAWP (mmHg)	7 [5–10]	8 [5–10]	0.2
mRAP (mmHg)	7 [3–11]	6 [2–9]	0.3
SVi (mL/m2)	30 [22–36]	38 [29–46]	**< 0.001**
CO (L/min)	4.2 [3.1–5.2]	5.2 [4–6.4]	**< 0.001**
CI ($L/min/m^2$)	2.1 [1.8–2.6]	2.9 [2.3–3.5]	**< 0.001**
PVR (WU)	10 [6–13]	5 [4–9]	**< 0.001**
Systolic NIBP (mmHg)	133 [121–148]	124 [111–134]	**< 0.001**
Diastolic NIBP (mmHg)	84 [75–95]	75 [68–83]	**< 0.001**

Data are expressed as median [inter-quartile range].
BSA, body surface area; CO, cardiac output; CI, cardiac index; HR, heart rate; LA, left atrium; LV, left ventricle; LVEDV, LV end-diastolic volume; LVESV, LV end-systolic volume; LVEF, left ventricular ejection fraction; mPAP, mean pulmonary artery pressure; mRAP, mean right atrial pressure; NIBP, non-invasive systemic blood pressure; PAWP, pulmonary artery wedge pressure; PVR, pulmonary vascular resistance; RA, right atrium; RV, right ventricle; RHC, right heart catheterization; RV inflow, right ventricle inflow diameter; RV mid, right ventricle midventricular diameter; RVFAC, RV fractional area change; RVFWS, right ventricular free wall strain; SVi, stroke volume index; sPAP, systolic pulmonary arterial pressure; S´, peak systolic velocity of the lateral tricuspid valve annulus; TAPSE, tricuspid annular plane systolic excursion; TR, tricuspid regurgitation; WU, Wood Units.
Bold values annotate $P < 0.05$.

Table 4 RVSWi by echocardiography and by right heart catheterization at baseline and follow-up visit

	Baseline ($n = 54$)	Short-term follow-up ($n = 44$)	Δ Values	*P*-value
$RVSWi_{ECHO\text{-}Max}$ ($mmHg*mL*m^{-2}$)	1839 [1402–2282]	1887 [1439–2505]	137 [−344–592]	0.4
$RVSWi_{ECHO\text{-}Mean}$ ($mmHg*mL*m^{-2}$)	1051 [784–1256]	1113 [867–1483]	118 [−196–345]	0.1
$RVSWi_{RHC}$ ($mmHg*mL*m^{-2}$)	1056 [832–1362]	1243 [795–1495]	114 [−156–243]	0,1

Data are expressed as median [inter-quartile range].
RVSWi, Right ventricular stroke work index; $ECHO_{-Max}$, echocardiography using systolic pulmonary arterial pressure and stroke volume index as input data; $ECHO_{-Mean}$, echocardiography using mean pulmonary arterial pressure and stroke volume index as input data; RHC, right heart catheterization; Δ values, Difference between short-term follow-up and baseline.

analyses were performed by commercially available software (IBM, SPSS Statistics, version 29, Chicago, IL, USA).

Results

Clinical characteristics

Demographics and patients' characteristics at baseline (54 patients) and short-term follow-up visits (44 patients) are shown in *Table 1*. The predominant cause of PAH was idiopathic. At baseline and follow-up visits of 146 [102–196] days, most patients were in WHO functional classes II and III with some improvement over time. 6MWT revealed short walking distance and NT-proBNP was elevated, yet both improved from baseline to follow-up (*Table 1*). Patients exhibited typical comorbidities for a PAH cohort. The majority (98%) of patients were initiated on PAH-specific treatments consisting of single or combination therapy (*Table 2*) of endothelin receptor antagonists, phosphodiesterase 5 inhibitors, and/or prostacyclin analogue therapy. Median outcome follow-up was 101 months (IQR, 84–127). During this time span 40 patients died, and one patient had undergone lung transplantation.

The median time between echocardiography and RHC was 0 days (IQR, 0–1 days), at both baseline and follow-up visits. Echocardiographic characteristics are shown in *Table 3*. At baseline, patients exhibited small LV volumes, normal LV ejection fraction, normal LA volumes, and enlarged RA. At follow-up, LA as well as LV volumes increased to normal values, while RA size did not change from baseline. At baseline, RV was enlarged with reduced RV function as measured by RVFAC and RVFWS. At follow-up, TAPSE, S', and RVFWS exhibited higher values, reaching values within the normal range.[31]

Tricuspid regurgitation was present as mild (60%) or moderate (40%) at baseline without significant changes at follow-up. Severe tricuspid regurgitation was not detected. TR velocities, and hence TR_{maxPG} and TR_{meanPG} decreased at follow-up ($P < 0.001$).

Haemodynamic characteristics and right ventricular stroke work index

Haemodynamic characteristics by RHC at baseline and follow-up visits are presented in *Table 3*. sPAP, mPAP, and PVR at baseline were 75 (68–88) mmHg, 45 [39–56] mmHg and 10 [6–13] WU, respectively, with low SVi and CI. All values improved at follow-up (*Table 3*).

RVSWi derived from echocardiography and RHC are shown in *Table 4*. $RVSWi_{ECHO\text{-}Max}$ was higher at baseline and at follow-up compared to $RVSWi_{RHC}$ ($P < 0.001$), whereas $RVSWi_{ECHO\text{-}Mean}$ did not differ from the invasive parameter at either baseline or follow-up ($P = 0.6$, $P = 0.5$). None of the RVSWi-derived methods differed significantly from baseline to follow-up.

Haemodynamics in patients grouped by RVSWi quartiles at baseline is presented in *Table 5* and Supplementary data online, *Figure S1*. The lowest quartile ($RVSWi < 839$ $mmHg*mL*m^{-2}$) had lower SVi than the other quartiles ($P < 0.05$) (see Supplementary data online, *Figure S1A*) with no difference in sPAP, mPAP, and PVR among quartiles (see Supplementary data online, *Figure S1C* and *D*). Highest SVi was noted in the group with the highest quartile (see Supplementary data online, *Figure S1A*).

Patients with WHO functional class IV had lower RVSWi than those with WHO functional class II ($P = 0.03$), with no differences among the remaining groups ($P > 0.05$) (see Supplementary data online, *Figure S2*).

RVSWi and mortality

At long-term follow-up, 40 patients had died. Non-survivors were older, had shorter 6MWT at baseline, and had significantly lower cardiac index by RHC (*Table 6*). None of the echocardiographic measures and neither RVSWi by any methods differed between survivors and non-survivors (*Table 6*).

In univariate Cox proportional hazard analysis, age >65 years and 6 MWT < 160 m were associated with outcome (*Table 7*). In the multivariate analysis, performed individually for each RVSWi parameter, including age > 65 years, 6MWT <160 m, and WHO classes III and IV, echocardiography-derived RVSWi were associated with all-cause mortality. Kaplan–Meier survival analysis stratified by RVSWi quartiles showed no differences in survival between the groups (*Figure 3*).

Discussion

In PAH, RVSWi did not differ from baseline to short-term follow-up visits with neither echocardiography-derived nor invasive methods. This was despite the initiation of PAH-targeted medication and subsequent substantial improvement in conventional haemodynamic parameters, 6MWT, and NT-proBNP. However, in multivariate analysis including age >65 years, 6MWT <160 m, and WHO classes III and IV, both echocardiography-derived RVSWi methods showed an association with mortality, while the invasive RVSWi did not. Yet the hazard ratios among the methods differed only marginally. To the best of our knowledge, this is the first study that has analysed invasive and echocardiography-derived RVSWi in follow-up assessment of adult patients with PAH.

RVSWi physiology

At baseline visit, our patients were in different stages of diseases. Some patients were in the incipient phases, when the right ventricle is still able to maintain an adequate SV despite increased PA pressure. Others were in a later phase of the disease, when the RV adaptative mechanisms were no longer efficient, resulting in an inadequate SV and a high preload state. It is important to acknowledge and understand that the RVSWi value can represent both a normal state or a balanced/unbalanced situation, when SV is low and PA pressure high, or the contrary

Table 5 Haemodynamic in patients grouped by RVSWi quartiles at baseline

Baseline RVSWi by quartiles	sPAP (mmHg)	mPAP (mmHg)	PVR (WU)	SVi (mL/min)
Quartile 1 ($n = 13$) RVSWi ≤ 839 mmHg*mL*m^{-2}	75 [46–90]	47 [33–53]	13 [7–16]	19.5 [18–26]***
Quartile 2 ($n = 14$) RVSWi 840–1061 mmHg*mL*m^{-2}	68 [48–87]	42 [30–53] *	10 [4–15]	27 [22–38]
Quartile 3 ($n = 14$) RVSWi 1062–1365 mmHg*mL*m^{-2}	82 [75–90]	53 [43–56]	10 [8–12]	29 [25–31]***
Quartile 4 ($n = 13$) RVSWi ≥ 1366 mmHg*mL*m^{-2}	76 [73–89]	45 [43–56]	8 [6–13]	38 [33–43]

Data are expressed as median [inter-quartile range].
RVSWi, right ventricular stroke work index; sPAP, systolic pulmonary arterial pressure; mPAP, mean pulmonary arterial pressure; PVR, pulmonary vascular resistance; SVi, stroke volume index.
*$P < 0.01$ (mPAP in quartile 2 vs. quartile 3), ***$P < 0.001$ (SVi in quartile 1 vs. quartile 4, SVi in quartile 3 vs. quartile 4).

Table 6 Differences in echocardiographic and invasive haemodynamic parameters at baseline between the survivors and non-survivors

	Survivors ($n = 14$)	Non-survivors ($n = 40$)	*P*-value
Clinical characteristics			
Age (years)	54 [36–64]	71 [64–76]	**<0.001**
6MWT (m)	378[231–446]	210 [90–321]	**<0.001**
HR (beats/min)	89 [78–97]	80 [71–93]	0.2
Systolic BP (mmHg)	134 [110–144]	134 [123–153]	0.8
Diastolic BP (mmHg)	93 [69–103]	83 [76–94]	0.8
Echocardiographic parameters			
RA area (cm^2)	21[15–27]	22 [18–26]	0.1
RV inflow (mm)	49 [39–55]	49 [44–56]	0.4
RV mid (mm)	37[28–48]	40 [31–44]	0.5
TAPSE (mm)	18 [14–19]	18 [14–21]	0.3
S`(cm/sec)	11 [8–12]	10 [8–12]	0.1
RVFAC (%)	28 [17–47]	26 [17–33]	0.3
RVFWS	13 [8–20]	16 [11–20]	0.7
TRmaxPG (mmHg)	74 [46–85]	70 [56–80]	0.3
TRmeanPG (mmHg)	46 [30–47]	40 [32–45]	0.6
RHC parameters			
sPAP (mmHg)	78 [48–97]	75 [68–88]	0.6
mPAP (mmHg)	50 [30–61]	44 [39–55]	0.9
SVi (mL/m^2)	25 [21–36]	30 [22–37]	0.7
CO (L/min)	4.2 [3.7–5]	4.1 [3.1–5.3]	0.05
CI (L/min/m^2)	2.4 [1.9–2.8]	2.1 [1.8–2.6]	**0.01**
mRAP (mmHg)	5.5 [2–12]	7 [3–10]	0.8
PVR (WU)	11 [5–15]	9 [7–13]	0.1
RVSWi			
$RVSWi_{ECHO\text{-}Max}$ (mmHg*mL*m^{-2})	1728 [1288–2185]	1874 [1428–2346]	0.5
$RVSWi_{ECHO\text{-}Mean}$ (mmHg*mL*m^{-2})	1036 [824–1160]	1064 [782–1327]	0.8
$RVSWi_{RHC}$ (mmHg*mL*m^{-2})	1038 [774–1428]	1070 [870–1358]	0.7

Data are expressed as median [inter-quartile range].
6MWT, six-minute-walk test; BP, blood pressure; CO, cardiac output; CI, cardiac index; ECHO, echocardiography; HR, heart rate; mPAP, mean pulmonary artery pressure; mRAP, mean right atrial pressure *P*-value; PG, pressure gradient; PVR, pulmonary vascular resistance; RA, right atrium; RV, right ventricle; RV inflow, right ventricle inflow diameter; RV mid, RV midventricular diameter; RHC, right heart catheterization; RVFAC, RV fractional area change; RVFWS, right ventricular free wall strain; RVSWi, right ventricular stroke work index; $RVSWi_{ECHO\text{-}Max}$, TR_{maxPG}×SVi_{ECHO}; $RVSWi_{ECHO\text{-}Mean}$, TR_{meanPG}×SVi_{ECHO}; $RVSWi_{RHC}$, ($mPAP_{RHC}$—$mRAP_{RHC}$)×SVi_{RHC}; SVi, stroke volume index; sPAP, systolic pulmonary arterial pressure; S´ peak systolic velocity of the lateral tricuspid valve annulus; TAPSE, tricuspid annular plane systolic excursion; TR, tricuspid regurgitation; WU, Wood Units.
Bold values annotate $P < 0.05$.

Table 7 Univariate and multivariate analyses of clinical, echocardiographic, and invasive baseline parameters regarding mortality

Baseline parameters	Univariate			Multivariate		
	HR	95% CI	*P*-value	HR	95% CI	*P* value
Male vs. female sex	1.17	0.602–2.276	0.642	—	—	—
Age >65 (years)	2.7	1.249–5.806	*0.01*	1.4	0.561–3.177	0.5
6MWT <160 m	2.1	1.108–4.222	*0.02*	2.1	0.959–4.801	0.06
WHO class III and IV[a]	2.1	0.919–4.771	*0.079*	2.8	0.974–8.322	0.05
RA area > 26 (cm2)	0.6	0.297–1.439	0.291	—	—	—
RA volume index (mL/m2)	1	0.971–1.002	*0.092*	0.9	0.981–1.002	0.1
TAPSE (mm)	1	0.995–1.097	0.516	—	—	—
S´ (cm/sec)	1	0.923–1.148	0.603	—	—	—
RVFAC (%)	1	0.969–1.028	0.902	—	—	—
RFWS (%)	1	0.949–1.141	0.4	—	—	—
TRmaxPG (mmHg)	1	0.986–1.030	0.491	—	—	—
TRmeanPG (mmHg)	1	0.977–1.060	0.417	—	—	—
sPAP (mmHg)	1	0.989–1.028	0.390	—	—	—
mPAP (mmHg)	1	0.979–1.040	0.549	—	—	—
SVi (mL/m2)	1	0.959–1.035	0.852	—	—	—
PVR (WU)	1	0.937–1.072	0.942	—	—	—
$RVSWi_{ECHO\text{-}Max}$ ($mmHg*mL*m^{-2}$)	1	1–1.001	*0.079*	1.001	1–1.002	**<0.001**
$RVSWi_{ECHO\text{-}Mean}$ ($mmHg*mL*m^{-2}$)	1	1–1.002	*0.051*	1.002	1–1.003	**<0.001**
$RVSWi_{RHC}$ ($mmHg*mL*m^{-2}$)	1	0.999–1.001	0.921	1	0.999–1.001	0.4

6MWT, six-minute-walk test; CI, Confidence interval; ECHO, echocardiography; HR, hazard ratio); mPAP, mean pulmonary artery pressure, *P*-value; PG, pressure gradient; PVR, pulmonary vascular resistance; RA, right atrium; RV, right ventricle; RHC, right heart catheterization; RVFAC, RV fractional area change; RVFWS, right ventricular free wall strain; RVSWi, right ventricular stroke work index; $RVSWi_{ECHO\text{-}Max}$, TR_{maxPG}×SVi_{ECHO}; $RVSWi_{ECHO\text{-}Mean}$, TR_{meanPG}×SVi_{ECHO}; $RVSWi_{RHC}$, ($mPAP_{RHC}$—$mRAP_{RHC}$)×SVi_{RHC}; SVi, stroke volume index; sPAP, systolic pulmonary arterial pressure; S´ peak systolic velocity of the lateral tricuspid valve annulus; TAPSE, tricuspid annular plane systolic excursion; TR, tricuspid regurgitation; WHO-FC, World Health Organisation- Functional capacity; WU, Wood Units.
Italic values annotate $P < 0.1$ in univariate analysis; bold values annotate $P < 0.05$ in multivariate analysis.

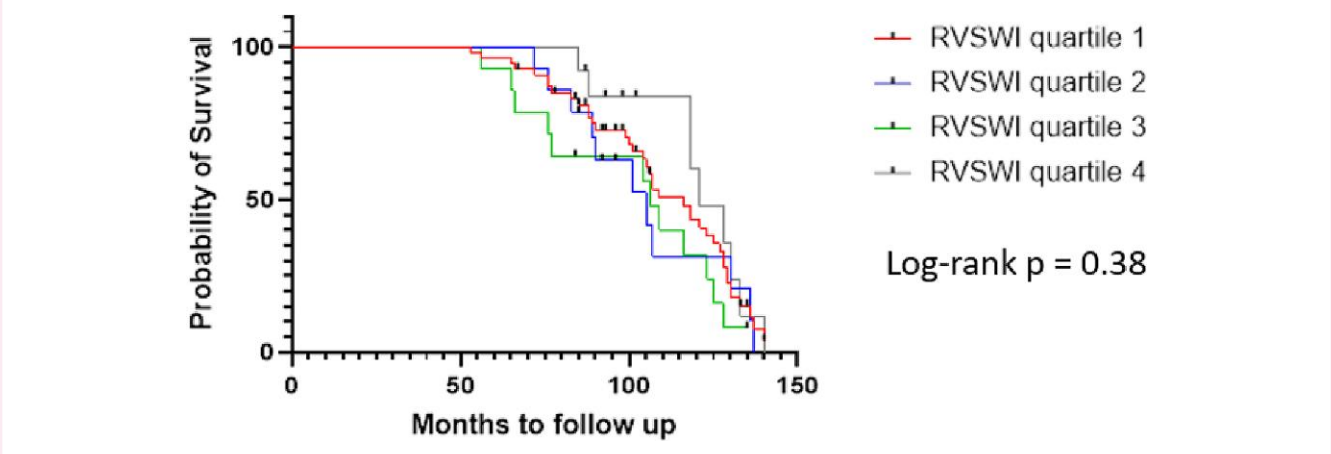

Figure 3 Kaplan–Meier survival curve stratified by quartiles of RVSWi. RVSWi, Right ventricular stroke work index; quartile 1 ($n = 13$), RVSWi ≤ 839 $mmHg*mL*m^{-2}$; quartile 2 ($n = 14$), RVSWi 840–1061 $mmHg*mL*m^{-2}$; quartile 3 ($n = 14$), RVSWi 1062–136i $mmHg*mL*m^{-2}$; quartile 4 ($n = 13$), RVSWi ≥ 1366 $mmHg*mL*m^{-2}$.

when SV is high and PA pressure low (as in normal haemodynamic) (see Supplementary data online, *Figure S3*). It is challenging to understand the value of RVSWi in clinical practice and longitudinal follow-up in PAH. It might strike as counterintuitive that the work performed by the RV is not changed after initiation of treatment. However, RVSWi is a product of afterload (pressure) and stroke volume. The intended reduction in afterload and increase in SV achieved by medical treatment from baseline to follow-up might therefore balance out when computing RVSWi.

Stroke work expresses the external work performed by the RV myocardium to eject blood and is hence in PAH a measure of the ability to generate stroke volume despite high afterload.[1–5]

In our cohort, surrogate indices of RV function improved at short-term follow-up, assessed by RHC (SVi_{RHC} and CI_{RHC}) and by echocardiography (TAPSE, RVFAC, RVFWS, and SVi_{ECHO}). As intended, RV afterload decreased at follow-up (sPAP, mPAP, PVR measured by RHC and echocardiography-derived sPAP and mPAP). At follow-up, the RV diameters decreased, and the LA and LV volumes increased, supporting a reduction in RV dilatation after treatment initiation. The reduction in RV dilatation is not significant, likely owing to the remaining highly elevated pulmonary pressures and not optimized medical treatment, yet at short-term follow-up. When PVR decreases and SVi increases owing to less pulmonary vascular obstruction, a possible explanation for LV and LA ameliorating in size, is due to normalizing flow to the otherwise underfilled left heart in PAH, as well as a concomitant right-sided volumetric decrease, reducing the interventricular dependence.

RVSWi defines the work performed by the RV by incorporating preload, afterload, and stroke volume.[16–18,21,22] Gold standard for computing stroke work is from pressure-volume loops.[32–34] (see Supplementary data online, *Figure S3*). Invasively, mPAP has typically been used for computing RVSWi.[16–21] Thereby, it is assumed a flat systolic ejecting part of the pressure-volume loop. The 'dome' in the systolic ejecting part is a substantial portion of the stroke work. The underestimation of stroke work is augmented in PAH, as both the domed part of the loop and the reflection wave typically noticed in PAH are not incorporated. One could argue that RVSWi based on mPAP reflects only a truncated computation of RVSWi. Thus, sPAP would be more correct to use.[33] This was embraced by a study assessing biventricular coupling index in precapillary pulmonary hypertension in which the authors adopted a simplified calculation of RVSWi using TR_{maxPG} without mRAP instead of the original formula including mPAP and RAP, as echocardiographic estimation of both mPAP and RAP is affected by limited reliability.[35,36]

Several algorithms have been proposed to estimate RAP through a combination of IVC size and collapsibility.[6,23] Brennan *et al.*[37] showed that traditional classification of RAP into 5 mmHg ranges had a 43% accuracy compared to invasive measurements. They noticed that with an IVC <21 mm and collapsibility <35% it is not possible to estimate RAP, due to the high range of variability of invasive measured RAP. Di Maria *et al.*[16] have proposed an echocardiographic formula for RVSWi in children with PAH, designed by multiplying the TR_{maxPG} with SVi using the stroke volume from the RV outflow tract. However, they did not incorporate mRAP in their formula. Since estimated sPAP is computed from adding mRAP to $TR_{max}PG$, and RVSWi is computed from (sPAP-mRAP)×SVi, by pure math it appears fair to include only $TR_{max}PG$ in the computation of RVSWi.

Low values of invasive RVSWi (<1450 mmHg*mL*m^{-2}) have been associated with death or readmission, and were interpreted as due to right heart failure.[27] Moreover, in patients with advanced left ventricular heart failure, low RVSWi in combination with high PVR inferred a higher risk for a biventricular assist device.[38] On the contrary, increased RVSWi in patients undergoing lung transplantation was indicative of higher mortality and prolonged intensive care stay.[18] High RVSWi values have also been related to worsened kidney function in patients with combined pre- and post-capillary pulmonary hypertension.[39]

Mortality and RVSWi

We retrospectively analysed patients at the first visit and 3–12 months after treatment initiation. Our patients were mainly in a compensated stage at inclusion, which improved WHO-FC, 6MWT, and proBNP at follow-up support. Still, in our cohort, 40 of 54 patients died (78%). This mortality is in alignment with national registries[40–44] and highlights that PAH prognosis remains poor and the high importance of optimizing treatment strategies and better timing for lung transplant.[44,45]

At baseline, RVSWi did not differ between the survivors and non-survivors. The patients with WHO functional class IV had lower RVSWi compared to those with a better WHO functional class. This is in line with a paediatric cohort of PAH, in which RVSWi was associated with abnormal WHO functional class, as well as mortality.[8,16,19]

In our population, echocardiography-derived RVWSi by multivariate analysis was associated with mortality while the invasive method was not., However, in univariate analysis, RVSWi was not associated with mortality. Yet, there are conflicting data regarding RVSWi and adverse events, and different cut-off values have been suggested to assess the role for the clinical use of RVSWi in risk assessment.[18,20,38,39] As such, the usefulness of RVSWi may still be controversial in adult PAH patients and the role in follow-up needs to better be defined in future studies.

Limitations

Some limitations should be noted. First, this is a retrospective study in a single PAH centre. The patients who have been referred and investigated might be highly selected. Yet, our centre is a tertiary centre with echocardiography and RHC as standard investigation, and referrals for investigation of PAH and chronic thromboembolic pulmonary hypertension (CTEPH) from the region are examined in our centre. Thus, this minimizes the risk of selection bias. Second, the cohort was small, not all patients were eligible for follow-up, and six patients died before the follow-up visit. For the patients that did not survive in our study, there was no significant difference in all the echocardiographic and invasive derived RVSWi parameters compared with the survivals. One should note that PAH is a rare disease and to obtain a large cohort study, a multicenter study would be favourable. Third, echocardiography and RHC were not performed simultaneously, but most patients were examined within the same day, and none had clinical deterioration or change in treatment between examinations. Fourth, RVSWi computation is prone to alteration when significant regurgitations or shunts are present. Yet, no significant aortic or pulmonary regurgitations were noticed and no patients with intracardiac shunts or severe tricuspid regurgitation were included. Fifth, the retrospective nature of the study is a caveat, and future prospective studies are warranted. Sixth, there is a lack of conformity in normal values for RVSWi; however, Ibe *et al.* suggested 375–768 mmHg*mL*m^{-2} as a normal range for healthy adults.[27] All RVSWi values in our study were well above these suggested normal values both at baseline and at short-term follow-up. Moreover, since no reference values have been established, comparison of absolute RVSWi values between patients is challenging and not recommended.

Conclusions

RVSWi did not differ from baseline to short-term follow-up in patients with PAH, despite substantial improvement in 6MWT, NT-proBNP, and conventional haemodynamic parameters after treatment initiation in adult patients with PAH. It could be presumed that the intended reduction of right-sided afterload and increase in SVi from baseline to follow-up balance out each other between these two time points. The baseline RVSWi methods were not associated with long-term mortality by univariate analysis. However, when adjusting for clinical variables using multivariate analysis a significant association between echocardiography-derived RVSWi and mortality could be detected, even if only discretely. RVSWi might instead be more useful in risk assessment in adult patients with PAH at a later and more decompensated stage of disease, and then preferably in selected cases where the patients should be their own reference.

Supplementary data

Supplementary data are available at *European Heart Journal - Imaging Methods and Practice* online.

Consent: Written informed consent was given by the patients allowing analysis of all their data, as granted in the ethical approval.

Conflict of interest: R.J: None, A.W.E.: None, A.I.: None. G.R. reports personal lecture fees from AOP Health/Orpha Care, Janssen, M.S.D., and Nordic Infucare outside the submitted work; and is or has been a primary investigator or co-investigator in clinical PAH trials for Acceleron, Actelion Pharmaceuticals Sweden AB, Acceleron, Bayer HealthCare, GlaxoSmithKline, Janssen, MSD, Pfizer and United Therapeutics and in clinical heart transplantation immunosuppression trials for Novartis. The companies had no role in the data collection, analysis, and interpretation and had no right to disapprove of the manuscript. C.C.M.: None, E.O.: None.

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Data availability

The datasets generated and analysed during the current study are not publicly available due to the small sample size and the risk of identifying individual participants but are available from the corresponding author on reasonable request.

Lead author biography

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